

## Risk of Non-Hodgkin's Lymphoma and Prediagnostic Serum Organochlorines: $\beta$ -Hexachlorocyclohexane, Chlordane/Heptachlor-Related Compounds, Dieldrin, and Hexachlorobenzene

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Increases in non-Hodgkin's lymphoma (NHL) incidence and mortality rates during the past few decades remain largely unexplained. Studies suggest that organochlorine pesticides may contribute to an increased risk of NHL. In 1974, serum samples were obtained from 25,802 participants in the Campaign Against Cancer and Stroke in Washington County, Maryland (USA), and cryopreserved for future study. We measured prediagnostic levels of chlordane, lindane ( $\gamma$ -hexachlorocyclohexane),  $\beta$ -hexachlorocyclohexane, transnonachlor, heptachlor, heptachlor epoxide, oxychlordane, dieldrin, and hexachlorobenzene in serum samples of 74 cases of NHL and 147 matched controls. Previously, we found an association between NHL and serum levels of total PCBs (polychlorinated biphenyls), but not DDT (dichlorodiphenyltrichloroethane) and related compounds. In this instance, there was no evidence of an association between NHL risk and serum levels of any of the individual lipid- and recovery-corrected organochlorines that we evaluated, nor of the summed chlordane-related compounds (transnonachlor, heptachlor, heptachlor epoxide, oxychlordane). These findings do not support the hypothesis that the organochlorine compounds included in this study are strongly linked to the development of NHL. The possibility of a weak association cannot be excluded by these data. **Key words:** chlordane, dieldrin, heptachlor, hexachlorobenzene, hexachlorocyclohexane, lindane, non-Hodgkin's lymphoma, organochlorine. *Environ Health Perspect* 111:179–183 (2003). [Online 15 November 2002] doi:10.1289/ehp.4347 available via <http://dx.doi.org/>

Observed rates of non-Hodgkin's lymphoma (NHL) incidence and mortality have increased markedly in the United States and other countries in the last three to four decades (1). The increase has been ascribed, in part, to changing diagnostic patterns, the use of immunosuppressive drugs, and increasing rates of HIV infection. However, a substantial fraction of the excess remains unexplained (2,3). Widespread exposures to organic solvents, pesticides, hair dyes, and other common chemicals have been suggested, and several of these factors have been linked with elevated NHL risk in case-control and other studies (4–6). In a hospital-based case-control study, Hardell et al. (7) found NHL risk to be associated with serum chlordane and related compounds. Population-based case-control studies have observed associations of NHL risk with self-reported agricultural exposure to specific organochlorine pesticides (8–10).

In this study, we measured prediagnostic concentrations of several organochlorine compounds in stored serum samples from patients with NHL and matched controls identified from a population-based prospective cohort established in 1974 in Washington County, Maryland (USA). We examined the association between risk of NHL and lipid-corrected serum concentrations of these compounds. An evaluation of the risk of

NHL with serum levels of polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT)-related compounds was previously reported (11).

### Methods

Detailed methods are reported elsewhere (11). In brief, cases and controls were identified from a population of 25,802 adults in Washington County, Maryland (USA), who enrolled in 1974 in the Campaign Against Cancer and Stroke (CLUE I), sponsored by the Johns Hopkins University School of Hygiene and Public Health (now the Bloomberg School of Public Health). A 15-mL blood sample and responses to a brief questionnaire were obtained at enrollment. Serum was stored at  $-73^{\circ}\text{C}$ . In 1989, a second blood-collection survey was conducted (CLUE II); approximately 25% of individuals enrolled in CLUE I also participated in CLUE II.

**Cases.** All incident cases of NHL were identified from the Washington County Cancer Registry. Cases were eligible for this study if they were a CLUE I participant with NHL [*International Classification of Diseases, 8th Revision* (ICD-8) code 200 or 202] (12) first diagnosed between 1 January 1975 and 31 May 1994, without a history of cancer, except for nonmelanoma skin cancer, before the diagnosis of NHL. Persons who had

migrated out of Washington County before diagnosis were not eligible.

We identified 87 eligible cases, among whom 76 had serum samples available for analysis in our study. Of these, 51 had slides available for pathology. On review, two cases were judged not to be NHL (one Hodgkin's disease and one hairy-cell leukemia). Thus, 74 cases were included in the study.

**Controls.** Two controls were matched to each case. Eligible controls were alive and without a history of cancer at the time of case diagnosis (except possibly nonmelanomic skin cancer). Matching criteria included race, sex, date of birth within 1 year, participation in CLUE (CLUE I only or CLUE I and CLUE II), date of blood-sample donation within 15 days, participation in private censuses conducted by the Johns Hopkins University Training Center for Public Health Research in 1963 and 1975, and location of stored serum (Hagerstown or Baltimore, MD, USA). If an adequate volume of serum was not available for a control ( $< 3\%$ ), another individual was selected, using the same criteria. We matched cases and controls according to participation in the respective CLUE cohorts to enable comparison, in other settings, of samples from individuals who provided blood samples in both studies.

**Organochlorine analysis.** Serum samples were grouped in sets of one case and two matched controls, in random order. Samples were thawed, aliquoted into 1.5-mL volumes, and immediately refrozen on dry ice. Nine quality-control sets of three samples each were prepared by staff at Johns Hopkins University. The first sample in each set was a replicate of pooled serum samples collected during the

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We thank B. Ellis (Battelle-SRA Inc.), R. Mann (Johns Hopkins University), S. Hoffman and J. Hoffman-Bolton (Johns Hopkins University), and E. Gunter (Centers for Disease Control and Prevention).

This research was supported in part by Department of Health and Human Services grants CA60754 and ES03819 and Research Career Award HL21670 (G.W.C.).

Received 24 May 2000; accepted 24 June 2002.

CLUE I survey from 10 persons who resided outside the study area and therefore were not enrolled in the cohort. The second and third samples in each set were paired replicates from nine pooled samples of two or three participants. We used the first sample in each quality-control set to calculate a between-set coefficient of variation (CV). We used the second and third samples in each set to calculate a within-set CV (13). The nine quality-control sets were assigned unused study numbers and interspersed among study samples to ensure blinded laboratory analyses.

Serum samples were analyzed under blinded conditions at the National Center for Environmental Health, Centers for Disease Control and Prevention (14). A reagent blank to check for contaminants and an internal laboratory quality-control sample (spiked bovine serum) (14) were analyzed with every 10 study serum samples. Solid-phase extraction was carried out, and each sample was analyzed on two separate gas chromatographs with electron-capture detection. The chromatographs used different columns (DB5 and DB1701; J & W Scientific, Folsom, CA) to reduce interference and improve selectivity. Results were obtained for two lindane-related compounds [lindane ( $\gamma$ -hexachlorocyclohexane) and  $\beta$ -hexachlorocyclohexane], four chlordane- or heptachlor-related compounds (henceforth chlordane/heptachlor: transnonachlor, heptachlor, heptachlor epoxide, oxychlordane), two aldrin-related compounds (dieldrin and endrin), hexachlorobenzene, and mirex. We also determined the serum concentrations of four DDT-related compounds and 28 PCB congeners. The serum sample from one control was not successfully analyzed, resulting in 73 complete case-control sets (one case, two controls) and one set with one case and one control for statistical analysis. Here we report results for grouped and single organochlorine compounds, total chlordane/heptachlor-related (transnonachlor, heptachlor, heptachlor epoxide, and oxychlordane), transnonachlor, heptachlor, heptachlor epoxide, oxychlordane,  $\beta$ -hexachlorocyclohexane, dieldrin, and hexachlorobenzene. Fewer than 10% of cases and controls had detectable levels of endrin,  $\gamma$ -hexachlorocyclohexane, and mirex, and findings are not reported.

Correction for total lipid in serum was applied to all analytical values. Serum samples were analyzed for total cholesterol and triglycerides, and total lipids were calculated by a standard formula to correct for differences in recent food intake (15). Lipid correction was applied to individual compounds. In addition, we corrected for laboratory recovery, using nonconcurrent published data for the analytical method that was used (14). We calculated total chlordane/heptachlor-related compounds by summing the lipid- and recovery-corrected

concentrations of transnonachlor, heptachlor, heptachlor epoxide, and oxychlordane. Before summing, values of these compounds were converted to their chlordane equivalents (transnonachlor  $\times$  0.9219, heptachlor  $\times$  1.099, heptachlor epoxide  $\times$  1.052, and oxychlordane  $\times$  0.9665).

We did not remove values below the formal method detection limit. This detection limit is designed to remove 99.86% of false-positive values; however, this restrictive definition also results in loss of valid data.

**Statistical analysis.** We first tested case-control differences in levels of organochlorine concentration by the Wilcoxon signed rank test. We used conditional logistic regression to analyze the association between risk of NHL and quartiles of total lipid- and recovery-corrected serum concentrations of eight organochlorine or grouped chlordane-related chemicals (based on the distribution among controls). Statistical significance was calculated by the likelihood ratio test based on the model. This results in deletion of all participants within a set when data are missing for either the case or both controls. Tests for trend were calculated by a variable equal to the mean organochlorine concentration in each quartile, divided by the mean concentration in the first quartile. Similar trend results were obtained with the organochlorine value as a continuous variable. Questionnaire data that we included in the analysis were as follows: years of education (< 12 years,  $\geq$  12 years), ever smoked cigarettes (yes/no), and currently smoking cigarettes (yes/no). We also included variables representing Epstein-Barr virus early antigen (EBV-EA) seropositivity and total PCB level (11).

The mean time to diagnosis among the 74 cases, after enrollment in the cohort in 1974, was 12.1 years (SD, 5.2; range, 1–20). Ninety-nine percent of cases and their 147 matched controls were Caucasian. Age at enrollment, sex distribution, and smoking habits were similar in each group. A higher proportion of cases (64%) than controls (50%) were high school graduates (12).

Using results from quality-control serum samples, we calculated interset (analyses

conducted on the same day) and intraset (separate days) CVs for six individual organochlorine compounds and a combined group of chlordane-related compounds. Intraset and interset CVs, respectively, were as follows:  $\beta$ -hexachlorocyclohexane, 0.19 and 0.36; chlordane/heptachlor-related compounds, 0.24 and 0.24; transnonachlor, 0.34 and 0.09; heptachlor epoxide, 0.33 and 0.26; oxychlordane, 0.34 and 0.47; dieldrin, 0.22 and 0.30; and hexachlorobenzene, 0.19 and 0.36. With minor exception, the levels of these compounds in our quality-control samples were above the limit of detection. In contrast, more than half the measured values of heptachlor were at or below the nominal detection limit (Table 1), and random variation in the extraction and analytical system contributed proportionally more to the elevated CVs observed. The intraset and interset CVs for heptachlor were 0.89 and 1.04.

In Table 1, summary data describing organochlorines in sera for cases and the average of the two controls in each set are described by the median value and 10th, 25th, 75th, and 90th percentiles. All values are lipid adjusted and corrected for recovery, using factors reported by Brock et al. (14). In Table 1, we also show results from a comparison of serum levels between cases and controls, using the Wilcoxon signed rank test. Except for  $\beta$ -hexachlorocyclohexane, there was no significant difference in lipid-adjusted and recovery-corrected level between the case and control series. The distribution of  $\beta$ -hexachlorocyclohexane was significantly elevated among cases compared with controls.

Odds ratios for increasing levels of organochlorines, stratified by quartile of lipid-corrected and recovery-adjusted level, are shown in Table 2. The referent level in each instance was the lowest quartile, with the exception of heptachlor, where tertiles were used and all determinations below detection were placed in the referent group. Confidence intervals included 1.0 for odds ratios of the seven individual compounds that we analyzed, as well as for the grouped chlordane-related compounds. The trend of risk with increasing level of each organochlorine (or grouped

**Table 1.** Distribution of lipid-corrected serum concentrations of organochlorine compounds among cases of NHL and matched controls [median (10th, 25th, 75th, 90th percentiles)].

Organochlorine (ng/g lipid) <sup>a</sup>	Cases (n = 74)	Controls (n = 147)	p-Value <sup>b</sup>
Chlordane/heptachlor-related	301.3 (167.9, 234.8, 502.7, 707.3)	335.2 (158.0, 232.2, 438.5, 605.2)	0.81
$\beta$ -Hexachlorocyclohexane	139.9 (71.1, 101.0, 218.1, 286.5)	138.0 (56.9, 84.9, 179.4, 219.3)	0.02
Transnonachlor	75.9 (7.6, 46.9, 109.7, 173.7)	75.1 (33.6, 54.0, 109.8, 139.6)	0.88
Heptachlor	0 (0.0, 0.0, 4.6, 10.9)	0 (0.0, 0.0, 5.9, 13.8)	0.28
Heptachlor epoxide	111.2 (31.9, 66.5, 162.9, 305.4)	103.6 (30.3, 55.7, 173.8, 237.6)	0.96
Oxychlordane	143.1 (66.4, 86.9, 204.7, 293.1)	134.8 (56.6, 86.5, 179.0, 228.0)	0.32
Dieldrin	129.9 (60.7, 89.2, 207.4, 252.8)	116.9 (64.6, 85.3, 163.0, 224.7)	0.26
Hexachlorobenzene	36.9 (22.0, 27.5, 48.3, 62.5)	33.7 (19.2, 25.7, 47.1, 63.6)	0.84

<sup>a</sup>All values are adjusted for mean recovery. <sup>b</sup>p-Value for difference between cases and controls from Wilcoxon signed rank test.

chlordane-related compounds) did not significantly differ from the null at the  $p < 0.05$  level. The risk of NHL showed an increase with serum level of hexachlorobenzene that was attenuated when the logistic model was adjusted for serum PCBs, EBV titer, and other factors. Data were also analyzed without correction for laboratory recovery, with similar results for all odds ratios and tests for trend.

## Discussion

In this nested case-control study, we examined the association between risk of NHL and prediagnostic serum levels of several organochlorine compounds. We found no evidence of association with NHL for any of the

compounds we examined:  $\beta$ -hexachlorocyclohexane, transnonachlor, heptachlor, heptachlor epoxide, oxychlordane, hexachlorobenzene, dieldrin, or summed chlordane-related compounds (transnonachlor, heptachlor, heptachlor epoxide, and oxychlordane). An association with  $\beta$ -hexachlorocyclohexane observed with a rank sum test between cases and controls was not confirmed by an analysis of the exposure-response relationship. These data do not support hypotheses of links with these compounds suggested by findings from case reports and interview and body-burden studies of NHL, other hematopoietic cancers, and related hematologic conditions such as aplastic anemia (7,8,16,17). The null findings

reported here pose a striking contrast with our earlier finding in this study population of a strong and consistent association of NHL risk with total serum PCBs (11).

The major strength of this study derives from the prospective collection of biologic samples in a nested case-control design in a general population setting. Differential bias from cases and controls could not have influenced the result because all sera were obtained and frozen many years before diagnosis, when participants were healthy. Our analytical method to measure organochlorines was designed to exclude many interfering compounds (14), and we corrected for serum lipids as well as compound-specific recovery

**Table 2.** Total lipid- and recovery-corrected concentrations of organochlorine residues and risk of NHL.

Quartile	Organochlorine concentration (ng/g lipid)			Cases (n = 74)	Controls (n = 147)	Matched OR (95% CI) <sup>e</sup>	Matched, adjusted OR (95% CI) <sup>d</sup>
	Range <sup>a</sup>	Mean <sup>a</sup>	Mean <sup>b</sup>				
Chlordane/heptachlor related (transnonachlor, heptachlor, heptachlor epoxide, oxychlordane)							
1	57.9–232.2	162.3	33.0	16	37	1.0	1.0
2	232.4–335.2	277.1	47.9	22	37	1.5 (0.6–3.3)	1.3 (0.5–3.1)
3	335.9–434.5	381.8	59.9	15	36	1.0 (0.4–2.3)	1.0 (0.4–2.6)
4	438.5–1070.7	594.0	96.3	21	37	1.5 (0.6–3.6)	0.8 (0.3–2.4)
<i>p</i> -Value (trend)						$p = 0.68$	$p = 0.47$
$\beta$ -Hexachlorocyclohexane							
1	0.0–84.9	50.8	0.30	12	37	1.0	1.0
2	85.6–138.0	110.8	0.77	25	37	2.3 (0.9–5.6)	3.0 (1.1–8.4)
3	138.7–177.3	159.4	1.18	12	36	1.1 (0.4–3.1)	1.0 (0.3–3.2)
4	179.4–302.0	217.7	1.81	25	37	2.2 (0.9–5.5)	1.5 (0.5–4.3)
<i>p</i> -Value (trend)						$p = 0.20$	$p = 0.96$
Transnonachlor							
1	0.0–53.8	31.9	0.22	22	36	1.0	1.0
2	54.0–74.6	64.9	0.47	13	37	0.5 (0.2–1.3)	0.4 (0.1–1.1)
3	75.1–109.0	89.5	0.69	21	37	0.9 (0.4–2.0)	0.6 (0.2–1.7)
4	109.8–505.9	163.0	1.25	18	37	0.7 (0.3–1.8)	0.3 (0.1–1.1)
<i>p</i> -Value (trend)						$p = 0.70$	$p = 0.16$
Heptachlor							
1	0.0–0.0	0.0	0.0	47	95	1.0	1.0
2	0.9–7.7	4.7	0.03	17	26	1.4 (0.6–3.2)	1.5 (0.6–3.7)
3	7.9–93.1	23.1	0.14	10	26	0.8 (0.3–2.0)	0.8 (0.3–2.2)
<i>p</i> -Value (trend)						$p = 0.49$	$p = 0.55$
Heptachlor epoxide							
1	0.0–54.3	33.5	0.23	18	36	1.0	1.0
2	55.7–100.7	78.6	0.57	14	37	0.8 (0.3–1.8)	0.7 (0.3–1.7)
3	103.6–170.8	135.2	0.99	26	37	1.4 (0.6–3.0)	1.4 (0.6–3.6)
4	173.8–453.3	253.8	1.92	16	37	0.9 (0.4–2.0)	0.4 (0.1–1.2)
<i>p</i> -Value (trend)						$p = 0.95$	$p = 0.18$
Oxychlordane							
1	0.0–86.5	54.9	0.38	19	37	1.0	1.0
2	89.1–134.8	112.0	0.78	15	37	0.8 (0.3–1.9)	0.6 (0.3–1.7)
3	137.3–179.0	156.6	1.15	18	37	1.0 (0.4–2.2)	0.6 (0.2–1.6)
4	181.3–452.3	237.5	1.87	22	36	1.2 (0.5–2.8)	0.7 (0.3–2.0)
<i>p</i> -Value (trend)						$p = 0.53$	$p = 0.64$
Dieldrin							
1	26.6–84.2	62.8	0.42	18	36	1.0	1.0
2	85.3–116.7	100.6	0.70	15	37	0.8 (0.4–1.9)	1.0 (0.4–2.7)
3	116.9–153.8	131.9	1.03	17	37	0.9 (0.4–2.1)	1.2 (0.4–3.0)
4	163.0–393.9	227.1	1.78	24	37	1.3 (0.6–2.8)	0.9 (0.4–2.4)
<i>p</i> -Value (trend)						$p = 0.35$	$p = 0.88$
Hexachlorobenzene							
1	6.8–25.7	20.1	0.14	13	37	1.0	1.0
2	25.8–33.7	29.6	0.23	17	37	1.5 (0.6–3.7)	1.1 (0.4–3.2)
3	33.9–45.2	38.4	0.29	24	36	2.2 (0.9–5.6)	1.2 (0.4–3.6)
4	47.1–220.0	64.3	0.49	20	37	1.9 (0.7–4.9)	1.0 (0.3–3.2)
<i>p</i> -Value (trend)						$p = 0.31$	$p = 0.87$

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

<sup>a</sup>Lipid- and recovery-corrected serum concentrations. <sup>b</sup>Uncorrected serum concentrations. <sup>c</sup>Conditional logistic regression of 73 sets containing one case and two matched controls and one set containing one case and one matched control. <sup>d</sup>Controlled for years of education (< 12 years,  $\geq$  12 years), ever smoked cigarettes (yes/no), currently smoking cigarettes, EBV-EA seropositivity, and quartile of PCB concentration.

efficiencies. All analyses were performed blindly with respect to case-control status and without knowledge of which samples were included for quality-control purposes. The serum values of the organochlorine compounds that we measured were comparable with levels found in other U.S. populations, after accounting for decreases in serum concentrations of most compounds since 1974, when our sera were collected (18,19). It is unlikely that outmigration from the study affected our results. A systematic sample of 4% of households provided an estimate of 1.5% outmigration per year in the approximate 10-year period between a census held in 1975 and 1 April 1985. In addition, for outmigration to influence our result, it would have to be differential with respect to future NHL diagnosis as well as serum level of one or more organochlorine compounds.

Despite the unique strengths of this study, interpretation of its generally null results should be tempered by several considerations. The CVs for the compounds of interest here, derived from randomly inserted quality-control samples, were somewhat larger than we previously found for PCB or DDT/DDE (dichlorodiphenyldichloroethylene) determinations (11). The variance introduced by the implied measurement error may have contributed to variability in odds ratios, possibly obscuring associations of relatively small magnitude. We lipid-corrected all organochlorine measures, based on the notion that the compounds of interest are highly lipophilic and that equilibrium is rapidly established between adipose tissue and serum lipid (19). Finally, it is possible that confounding was present in this study and obscured associations of organochlorines with risk of NHL. This would be the case if etiologically relevant factors were inversely associated with the organochlorines we examined.

Animal bioassays have indicated the carcinogenicity of several compounds that were the focus of this study. Using a widely accepted classification scheme, expert committees convened by the International Agency for Research on Cancer have cited "sufficient evidence," based on evidence from laboratory animals, for carcinogenicity of chlordane/heptachlor, hexachlorobenzene,  $\alpha$ -hexachlorocyclohexane, and technical grade hexachlorocyclohexane (20,21). There is "limited evidence" for carcinogenicity of dieldrin,  $\gamma$ -hexachlorocyclohexane, and  $\beta$ -hexachlorocyclohexane (20,21). Although the epidemiologic evidence is far from definitive, there are suggestions that one or more of these compounds are human carcinogens and may be related to elevated risk of NHL. Farmers, who have generally elevated exposures to many of the compounds under consideration, are at elevated risk of NHL in many studies (22,23).

Chlordane was linked with NHL in a case-control study in the midwestern United States (9). Hematopoietic cancer deaths were not in excess in a small cohort of workers employed in the manufacture of chlordane and heptachlor (24). In a hospital-based study, Hardell et al. (7) found an association of NHL with postdiagnostic adipose tissue levels of six summed chlordane compounds among 27 patients and 17 hospital-based controls, with an especially strong association for transnonachlor. We were not able to confirm Hardell et al.'s findings in the present population-based study based on prediagnostic serum chlordane among 74 NHL cases and 147 controls. In our data, serum transnonachlor had a weak negative association with NHL risk.

Hexachlorocyclohexane, produced by photochlorination of benzene, results in  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and other isomers (25). Lindane, the  $\gamma$ -isomer, is used as an insecticide. However, little bioaccumulation of lindane occurs. We detected it in only 5% of serum samples, an insufficient number for statistical analysis. The  $\beta$ -isomer of hexachlorocyclohexane is more stable. It bioaccumulates in adipose tissue and was found in more than 90% of our serum samples, with a median concentration among controls of 138.0 ng/g lipid. Case reports describe the occurrence of aplastic anemia and other blood dyscrasias after lindane exposure (17,26-28). The carcinogenicity of lindane is less clear in humans than in laboratory animals. The strength of associations of NHL with lindane exposure, in data pooled from population-based case-control studies in four midwestern states, were decreased after adjustment for potential confounding from 2,4-dichlorophenoxyacetic acid (2,4-D) and diazinon (29). The carcinogenicity of the  $\beta$ -isomer is less clear. In this study, we did not observe an association of NHL with prediagnostic serum  $\beta$ -hexachlorocyclohexane level.

Although cancer mortality has been studied in several occupational groups exposed to aldrin and dieldrin, cohorts were small and the studies lacked sufficient statistical power to observe any but the strongest carcinogenic effects for relatively rare cancers such as NHL (30-34). Two small case-control studies of leukemia and lymphoma examined levels of aldrin/dieldrin in the bone marrow at diagnosis, with no observed differences (35,36). Likewise, data on carcinogenic effects of hexachlorobenzene in human populations are limited. Elevated cancer prevalence was noted among male chemical workers with elevated levels of serum hexachlorobenzene (37). Micronuclei were in excess in peripheral lymphocytes from 41 workers exposed to hexachlorobenzene and other compounds (38). No differences in hexachlorobenzene levels were found in the bone marrow of 13 leukemia or lymphoma patients and 16

healthy adult controls (35). We found no association between NHL risk and serum levels of either dieldrin or hexachlorobenzene.

In summary, we found no consistent differences in prediagnostic serum levels of several organochlorine compounds among NHL patients and matched controls in a population setting. Our results are reassuring in providing some evidence against a strong, consistent association between NHL and serum levels of the compounds that we analyzed at levels found in the general population. Our results, however, do not exclude the possibility of weaker associations that may be important in more highly exposed populations, such as agricultural workers.

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